UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/611,419	07/06/2000	Leonard A. Smith	067252.0105	6819

7590 03/31/2005

Baker Botts LLP
Attn Laurence H Posorske
The Warner Suite 1300
1299 Pennsylvania Avenue NW
Washington, DC 20004-2400

EXAMINER	
PORTNER, VIRGINIA ALLEN	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 03/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/611,419	SMITH ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-51,53,55,56,82,85 and 86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-51,53,55,56,82,85 and 86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 42-51,53, 55-56, 82 and 85-86 are pending.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 8,2003 has been entered.

Rejections Withdrawn

2. Claims 42-43 are no longer rejected under 35 USC 101, in light of the claim amendments reciting the phrases: "recombinant host cell" and "isolated or purified".
3. Claim 42 objected to because of the following informalities has been obviated in light of the fact that claim 42 no longer depends from claim 43.
4. The obviousness type double patenting rejection has been obviated through submission of an effective terminal disclaimer over claims 1-4, 5, 13-16 and 22 of US Pat. 6,495,143.
5. Claims 53 and 43 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention have been obviated in light of the amendments to the claims and remarks made of record.
6. In light of the new rules for incorporation by reference to essential material and the amendment of the first sentence of the instant Specification, changing the priority claim to include Application serial number 08/123,975 the New Matter, and lack of written description rejections under 35 USC 112, first paragraph rejections are herein withdrawn.

Claim Objections

7. Claims 50-51 and 55-56 are objected to because of the following informalities:

8. The recitation of the term "organism" in claims 50-51 is not further limiting of claim 48, which recites the terms "E.coli, yeast and a mammalian cell" ; an organism need not be a microorganism, and broadens the scope of the dependent claims.

9. Claims 55-56 have been amended to recite the phrase "of claim claim 42". The second recitation of the term "claim" is duplicative. Appropriate correction is required.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claim 49 recites the limitation "recovering from said transfected cell at least one insoluble polypeptide" in an effort to further limit claim 48, but the cell of claim 48 only expresses the nucleic acid, and the term "insoluble polypeptide" lacks antecedent basis in claim 48 that only transfect and expressed the nucleic acid; the nucleic acid need only be produced, and not translated into a polypeptide in the claimed method of claim 48, and even if the were to recite a polypeptide that could be translated from the expressed polypeptide, the term "insoluble" lacks antecedent basis in the independent claim. There is insufficient antecedent basis for this limitation in the claim. What are the structural components that make the polypeptide insoluble in light of the fact that botulinum toxins are water-soluble proteins (see Leduc et al, 1994, abstract, page 1095, line 4). While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed.

12. Claims 50 and 51 recite the phrase "wherein said organism" and depends from claim 48 which recites the term "cell"; the term "organism" lacks antecedent basis in claim 48 from which it depends. An organism need not be a microorganisms or a single cell. No transformed organisms such as a mouse are recited in the claims. What is claimed are transfected cells "E.coli, yeast and mammalian" cells in culture.

13. Claim 53 recites the phrase "isolating from said transfected cell at least one insoluble polypeptide"; the phrase "insoluble polypeptide" lacks antecedent basis in claim 53. The step

just prior to the isolating step is "culturing" so the "nucleic acid is expressed" but no polypeptide is required to be translated, nor is the encoded polypeptide required to be structured in such a way that if translated into a polypeptide that it would be insoluble.

14. Claims 55-56 recite the limitation "the AT content" and depend from claim 42, which recites SEQ ID NO 4 which is amino acid sequence. The phase "the AT content" lacks antecedent basis in claim 42 from which they depend. There is insufficient antecedent basis for this limitation in the independent claim from which they directly or indirectly depend.

15. Claims 85-86 recite the limitation "said polypeptide is at least 0.75% (w/w) of the total cellular protein" or"said polypeptide is at least 20.0% (w/w) of the total cellular protein" , respectively and depend from claims 82,45 and 42 which do not provide antecedent basis for the phrase "total cellular protein", in light of the fact that claims 42 and 45 are directed to nucleic acid sequences, and while claim 82 recites the term "host cell", the nucleic acid in the host cell, while being capable of being expressed, has not been expressed, as claim 45 is not required to be constitutively expressing the encoded polypeptide to any specific level. Therefore, claim limitations recited in claims 85-86 which depend from claims directed to nucleic acid compositions and sequences that can be expressed, none of the claims provide antecedent basis for the expressed polypeptide and for determining total cellular protein. The term "protein" also lacks antecedent basis in all of the claims which recite the term "polypeptide". While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this

subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

17. Claims 42-44, 45-47, 55 and 82 are rejected under 35 U.S.C. 102(b) as being anticipated by Kurazono et al (July 1992) as evidenced by Dertzbaugh et al, and Binz et al sequence Swiss Prot accession number P10845.

Kurazono et al disclose the instantly claimed invention directed to:

Instant claims 42-44: an isolated or purified nucleic acid (see page 14722, col. 2, paragraph 6 "Hc fragment from BoNt/A", the nucleic acid sequence encoding the polypeptide Hc region of amino acid residues for positions 872 to 1296 (see page 14728, col. 1, last two lines), the amino acid sequence comprising at least one epitope.

Instant claims 45-47: The isolated and purified nucleic acid that encodes at least one epitope of SEQ ID NO 4, was cloned into BamHI digested pSP73 to yield pMQ9, the plasmid comprising an expression control sequence which provided for the in vitro transcription and translation of the nucleic acid (see page 14722, col. 2, last full paragraph), wherein the expression control sequence present in the plasmid controlled expression of the cloned nucleic acid, and served to enhance expression of the nucleic acid, as it was transcribed and translated into a polypeptide product; the cloning expression vector being pSP73 (see page 14722, paragraph 1, bottom of first paragraph, "pSP73 vector(Promega; Krieg and Melton, 1988)" and page 14722, last paragraph).

Instant claims 55: wherein the AT content is less than about 70% (includes values above 70% or below 70% based upon the recitation of "about", which can be read to include 10% variation from the recited number and includes 77% or less), of the total base composition (the AT content of botulinum neurotoxin A Hc domain has the percentage AT content naturally based upon the bacterial codon bias). See page

14724, col. 2, middle of last paragraph: "mRNA derived from clostridial genes containing about 73% A+T in the coding region"

Instant claim 82: Kurazono et al disclose a recombinant host cell (see Figure 9, page 14728) comprising the nucleic acid of claim 45, wherein the mRNA was introduced into an Aplysia host cell (see page 14728, col. 1, lines 1-4) by microinjection (see page 14728, col. 2, paragraph 1 "Hc specific mRNA was injected into the same neuron"), and the mRNA functioned to complement the biological function of the light chains which had been introduced into the cell. Upon introduction of the coding sequence for the Hc fragment into the host cell, a biological effect was induced, specifically "an immediate onset of depression of the post synaptic response (page 14728, col. 2, paragraph 1, last 4 lines)".

Binz et al 's sequence (see Kurazono et al page 14728, col. 1, last lines bridging to col. 2, paragraph 1) which was used by Kurazono et al to produce the coding nucleic acid sequence, encodes the amino acid sequence of Swiss-Prot accession number P10845, and evidences of identity with the amino acid sequence of SEQ ID NO 4 (amino acid sequence), and is encoded by SEQ ID NO 3. Dertzbaugh et al provides evidence that the Hc region of amino acids encoded by the nucleic acid of Kurazono et al encodes at least 4 epitopes (see Dertzbaugh et al, Table 1, and Figure 1 showing antibodies).

1. Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

2. Inherently the reference anticipates the now claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states AArtisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior arts functioning, does not render the old composition

patentably new to the discoverer. AThe Court further held that Athis same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art.

18. Claims 42-50, 53, 55, 82 are rejected under 35 U.S.C. 102(b) as being anticipated by LaPenotiere et al (May 11-13, 1992, disclosure presented at the International Conference on Botulinum, Tetanus, Neurotoxins: Neurotransmission and Biomedical Aspects, Madison, Wisconsin) as evidenced by the New England Biolabs product description of pMal (see LaPenotiere et al, page 464, paragraph 2, line 2)

LaPenotiere et al disclose the instantly claimed invention directed to :

Instant claims 42-44, 55: an isolated nucleic acid of Botulinum toxin type A (see page 464, paragraph 2, "The DNA clone coding for the Hc domain of C. botulinum toxin serotype A was pCDA3"), Hc fragment (see page 463, Title "molecular engineered vaccine", Methods, page 464, paragraph 2 "PCR amplify the Hc region of the C.botulinum clone pCBA3"), wherein the expressed Hc fragment polypeptide induced a protective immune response (see page 465, middle of page "Immunization Trials"), and therefore comprised immunogenic epitopes.

Instant claim 45: the isolated nucleic acid was inserted into an expression vector, which contained expression control sequences (see page 464, paragraph 2, "Expression vectors pMal"), translation initiation signals present in the plasmid pMal

Instant claim 46-47: the nucleic acid further comprised an expression control sequence operatively linked to the nucleic acid (see page 464, paragraph 4 "IPTG-induced recombinant pMAL" (Ptac promoter is a strong promoter that expresses large amounts of encoded polypeptide, New England Biolabs product description for pMal)). The presence of the

expression control sequence provided for the expression of the encoded nucleic acid upon induction with IPTG through use of a promoter induced by IPTG.

Instant claim 82: the expression vector was inserted into E.coli host cell K12 DH5a (see page 464, paragraph 2, line 1).

The method of preparing a polypeptide comprised the steps of:

Instant claim 48, 53: **Transfecting** a cell with a nucleic acid encoding a polypeptide having ate least one immunogenic epitope of SEQ ID NO 4 (see page 464, paragraph 2 and page 465, Immunization Trails);

Culturing the transfected cell under conditions wherein the nucleic acid is expressed (see page 464, "E.coli cultures", paragraph 4, line 1);

Instant claim 49, 53: further comprising the step of recovering at least one insoluble polypeptide (see page 464, paragraph 4, line 5 "insoluble product" and the polypeptide was administered to a host animal (see page 465, paragraph 2, "amylase column-purified expression product).

Instant claim 50: wherein the host cell is Escherichia coli (see page 464, paragraph 2, line 1).

3. Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594
4. Inherently the reference anticipates the now claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states AArtisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior artσ functioning, does not render the old composition patentably new to the discoverer. AThe Court further held that Athis same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art.

19. Claims 42-45, 48, 50, 55, 82 rejected under 35 U.S.C. 102(b) as being anticipated by Thompson et al (1990).

Thompson et al disclose:

Instant claims 42-44: an isolated (see page 75, col. 2, paragraph 2, "isolated"; also see page 74, col. 1, paragraph 2, line 3 "isolated") and purified nucleic acid that comprises at least one epitope encoded by SEQ ID NO 4 and a nucleic acid sequence of SEQ ID NO 3 (see Figure 3, page 76),

wherein the nucleic acid sequence encoded the Botulinum toxin type A, C-fragment of the heavy chain (see page 75, Figure 2, plasmid "pCDA3" and col. 1, paragraph 2).

Instant claim 45: was cloned into a cloning vector (Figure 2, page 75, "pCBA3" a plasmid, inserted into and E.coli host cell (see page 73, col. 2, paragraph 4, bridging to page 74, first paragraph), wherein the nucleic acid sequence comprised an expression control sequence (see page 76, top of page "-35" and "–10" and "rbs" a ribosome binding site (see ledger at bottom of page 76, for Figure 3)).

Instant claim 55: the nucleic acid comprised less than about 70% d(A/T) content (see page 78, col. 1,paragraph 4, line 3 (70%)). The recited range includes 70% and is therefore disclosed in the applied reference.

Instant claim 82: The recombinant E.coli host cell comprises the nucleic acid sequence of claim 45: (see Materials and Methods section, E.coli host, page 73, col. 2, paragraph 4).

Instant claims 48 and 50: The reference also discloses a method of preparing a polypeptide, the method comprising the steps of :

Transfecting a cell with a nucleic acid encoding a polypeptide that comprising an amino acid sequence that is at least one epitope of SEQ ID NO 4 (see Figure 3, ledger narrative, see Figure 2, page 75; see page 74, "Recombinant clones" (col. 1, paragraph 3, bottom half); see page 73, col. 2, "E.coli host", last two lines); and

culturing the cell under conditions that the nucleic acid is expressed (E.coli cultured in L-broth, see page 74, col. 1, paragraph1), wherein the host cell was a gram-negative bacterial cell, specifically E.coli. Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594. Also see Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. The Court further held that Athis same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art.

Conclusion

1. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.
2. LaPenotiere et al (1995) is cited to show the Hc fragment sequence was contained in pCFA3 of Thompson et al , 1990, see page 1384, paragraph 3, line 8 and whole paragraph.
3. Carroll (US Pat. 5,196,193) is cited to antivenoms of toxins, and teach botulinum toxin to be a neurotoxin (see co.. 2, lines 43-47).

4. Clayton et al (1995) is cited to show a recombinant Clostridium botulinum neurotoxin serotype A synthetic gene expresses in E.coli.
5. Roberts et al (EP 0639081) is cited to show a mutant Salmonella strain that recombinantly expresses Clostridium tetani toxin C-fragment (see page 3, [0022] and abstract).
6. Rosenberg et al (1997) is cited to show Hc domain epitopes of botulinum toxin A and antibodies thereto.
7. Szabo, EA et al (1993) is cited to show Clostridium botulinum neurotoxin polymerase chain reaction reagents for Types A to E.
8. Uhr et al (US Pat. 4,664,911) is cited to show conjugates of toxin B chains, to include botulinum toxin (see abstract and col. 5, line 6).
9. Williams (WO91/13090) is cited to show a chmeric diphtheria toxin .
10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
March 21, 20

LRFS

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600